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DATE MAILED: 05/02/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(C) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-31 are pending in the application.
   Of the above, claims 13-27, 29 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-12, 28, 30, 31 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-31 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Part III: Detailed Office Action

Restriction Requirement:

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-12, 28, 30 and 31, drawn to mpl ligands, fusions thereof and compositions comprising, classified in Class 530, subclass 350.

II. Claims 13 and 14, drawn to antibodies and hybridomas, classified in Class 530, subclass 387.1 and Class 435, subclass 240.27.

III. Claims 15-25, drawn to nucleic acids encoding mpl ligands, host cells, and method of making mpl ligand protein, classified in Class 536, subclass 23.5 and Class 435, subclasses 69.1, 240.1, 252.3 and 320.1.

IV. Claim 26, drawn to a hybridization assay, classified in Class 435, subclass 6.

V. Claim 27, drawn to a nucleic acid amplification method, classified in Class 435, subclass 91.2.

VI. Claim 29, drawn to a method of treatment using mpl ligand, classified in Class 514, subclass 12.

The inventions are distinct, each from the other because of the following reasons:

The proteins of Invention I are related to the antibodies of Invention II by virtue of being the cognate antigen, necessary for the production of the antibodies. Although the protein and antibody are related due to the necessary stearic complementarity of the two, they are distinct inventions because the protein can be used another and materially different process from the use for production of the antibody, such as in a pharmaceutical composition in its own right as evidenced by claims 28, 30 and 31, or to assay or purify the mpl receptor (as the protein an mpl ligand), or in assays for the identification of agonists or antagonists of the receptor protein.

The fusion proteins and compositions of Invention I, which comprise other proteins, are related the antibodies of Invention II as independent and distinct compositions, wherein each is not required to produce the other, and the various compositions have distinct properties and uses.

The nucleic acids of Invention III are related to the protein of Invention I by virtue of

encoding same. The DNA molecule has utility for the recombinant production of the protein in a host cell, as recited in claims 28, 30 and 31. Although the DNA molecule and protein are related since the DNA encodes the specifically claimed protein, they are distinct inventions because the protein product can be made by another and materially different process, such as by synthetic peptide synthesis or purification from the natural source; it is for this reason that the host cells and methods of invention III are also distinct from the proteins of invention I. With respect to the fusion proteins of invention I, the Examiner notes that such do not require recombinant production; the proteins may be isolated from their respective natural sources (or synthesized) and then fused via chemical means, or simply chemically synthesized as a fusion protein. Further, the DNA may be used for processes other than the production of the protein, such as nucleic acid hybridization assay or amplification method, as evidenced by claims 26 and 27.

The products and compositions of Invention I are independent and distinct from the methods of each of inventions IV and V, wherein each is not required for the other.

Inventions I and VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the claimed product may be used for the production of the antibodies and hybridoma cells of Invention II.

The compositions of Invention II are related to the nucleic acids, vectors, and host cells of Invention III, as independent and distinct compositions, wherein each is not required to produce the other, and the various compositions have distinct properties and uses.

Invention II is related to each of the methods of inventions III-VI as product(s) and unrelated methods of using different products. As none of Inventions III-VI requires the compositions of Invention II, nor vice versa, they comprise independent and distinct inventions.

The nucleic acids of Invention III is related to each of inventions IV and V as product and processes of use. The inventions can be shown to be distinct if either or both of the following

can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the claimed product may be used in either of the distinct process of Inventions IV or V, or for the recombinant production of the encoded protein. Inventions IV and V are related to each other as independent methods of using a common product, wherein neither method requires the other.

The methods of Inventions III, IV and V are related as independent methods of using a common product. As none of the methods requires any of the other methods and as the various methods have different processes, purposes and endpoints, they are independent and distinct.

The methods of Inventions III and VI are related as method of making a product and method of using that product. As the method of making is distinct from the product itself, for reasons cited above, it follows that the method of making the product is independent of its method of use, as neither method requires the other.

Inventions IV and V are each related to Invention VI as distinct methods of using distinct products. As Invention VI does not require the methods of either Invention IV or V, nor vice versa, they are independent.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Darryl Winter on 4/10/95 a provisional election was made with traverse to prosecute the invention of group I, claims 1-12, 28, 30 and 31. Affirmation of this election must be made by applicant in responding to this Office action. Claims 13-27 and 29 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition

under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Formal Matters:

The disclosure is objected to because of the following informalities. Appropriate correction is required for each item:

(1) At page 16, line 12 the specification states that SEQ ID NO:1 and Figure 8 represent the "mature human *mpl* ligand"; however, it is noted that SEQ ID NO:1 includes the leader sequence, and the Examiner believes the correct reference would be to SEQ ID NO:6.

(2) Figure 10 and SEQ ID NO:8 are described at page 19 of the specification as showing the coding DNA sequence for murine mpl ligand, however both sequences include non-coding regions. Further, it is noted that the numbering of amino acids in SEQ ID NO:1 does not correspond with that of Figure 8, nor does SEQ ID NO:9 correspond in numbering of amino acids with Figure 10.

(3) The Specification should also be carefully reviewed for spelling and grammatical errors. For Example, at page 33, line 11, "possess" is misspelled. At page 36, line 3, "protein" is misspelled, at line 10 "sieve" is misspelled, and at line 17, "publishers" is misspelled. At page 39, line 1 "further" is misspelled. At page 45, line 13 "significantly" is misspelled.

(4) The blanket incorporation (as found at page 75) of all references cited in the disclosure is improper. Numerous publications are incorporated in their entirety without indication of the portions of said documents that are relevant. In the absence of evidence to the contrary, the Examiner considers that all such references contain material essential to enablement of the application. Essential matter may not be incorporated by reference to other than U.S. Patent documents or allowed U.S. Patent applications. See M.P.E.P. 608.01(p).

(5) At page 12, lines 12-13 the specification states "common ß-subunit for the three α-subunits IL-3Rα and GM-CSF-R"; it would appear that there are two, not three α subunits which utilize the common ß.

The deposit of biological organisms is not considered necessary for enablement of the

invention as it is currently claimed. The Examiner acknowledges deposit of biological material under ATCC accession number CRL 69575 (see specification, page 102).

Double Patenting Rejections:

Claim 1 is provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claim 1 of copending application Serial Nos. 08/176553 and 08/196689. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

Claims 1-12 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-6, 8, 9, 11, 12, 14 and 17 of copending application Serial No. 08/249376. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

Claims 2-11 and 28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 19 and 20 of copending application Serial No. 08/176553. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application encompass and overlap the claims of the instant application by inclusion of all *mpl* ligands, including those meeting the limitations of the instant claims. However, the copending claims may be infringed without infringing some of the instant claims due to the lack of limitation to the sequence of Figure 8 in the case of instant claim 6, the use of different biological assays (e.g. compare instant claim 5 to copending claim 2), and because in the case of claim 7, the copending application recites a broader group of species, although the glycosylation limitation is the same.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-11, 28, 30 and 31 are directed to an invention not patentably distinct from claims 1-4, 6, 7, 24, 26 and 27 of commonly assigned application Serial No. 08/185607.

Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application encompass and overlap the claims of the copending application by inclusion of all *mpl* ligands, including human. However, the instant claims may be infringed without infringing the copending claims due to the lack of limitation to "human" ligands.

Commonly assigned application Serial No. 08/185607, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

Claims 1-11, 28, 30 and 31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6, 7, 24, 26 and 27 of copending application Serial No. 08/185607. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application encompass and overlap the claims of the copending application by inclusion of all *mpl* ligands, including human. However, the instant claims may be infringed without infringing the copending claims due to the lack of limitation to "human" ligands.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 2-11, 28, 20 and 31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 24, 26 and 27 of

copending application Serial No. 08/196689. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application encompass and overlap the claims of the copending application by inclusion of all *mpl* ligands, including those with the sequence and other limitations found in the copending application, and the claims of the instant application are similarly encompassed and overlapped by those of the copending application by inclusion of all *mpl* ligands in the copending application. However, the instant claims may be infringed without infringing the copending claims due to differing sequence limitations.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention

was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-11, 28, 30 and 31 are provisionally rejected under 35 U.S.C. § 103 as being obvious over copending application Serial No. 08/185607 for reasons cited above. Although the claims of the copending application are of different scope than those of the instant application, the two applications are clearly drawn to the same subject matter.

Copending application Serial No. 185607 has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. § 102(e) if patented. This provisional rejection under 35 U.S.C. § 103 is based upon a presumption of future patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 C.F.R. § 1.132 that any unclaimed invention disclosed in the copending application was derived from the inventor of this application and is thus not the invention "by another", or by a showing of a date of invention prior to the effective U.S. filing date of the copending application under 37 C.F.R. § 1.131.

Objections/Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The current specification as filed fails to adequately describe what is meant by "*mpl* ligand polypeptide." There is adequate definition in the specification of the term "*mpl* ligand" (see page 21), however the Examiner can find no definition of the term "*mpl* ligand polypeptide". The word polypeptide is used variously in the art to refer to any protein, or fragment of any protein which consists of more than a few residues. The absence of an indication in the specification as to what applicants intend the term *mpl* ligand polypeptide to designate (that is, is this a full-length *mpl* ligand homologous to the proteins disclosed in the instant specification, or do applicants intend to also claim any fragment thereof which may or may not be an *mpl* ligand in and of itself) results in a failure of the current specification as filed to provide an adequate written description of the invention as it is currently claimed.

The current specification as filed also fails to adequately describe the invention because it is disclosed at page 34, lines 20-22, that the invention includes prepro-*mpl* ligand and pro-*mpl* ligand, however there is no description of what type of processing occurs *in vivo,* therefore no prepro- or pro- versions of the protein have been clearly described, and indeed the very identity of what constitutes "mature" *mpl* ligand is thrown into question. It is noted that proteins which occur in prepro- form (even after a secretory leader is removed) comprise a mature protein, as well as two additional portions which are successively cleaved from the protein to yield the mature protein. The "pro" form of the protein comprises the mature protein and one such additional portion. The current specification as filed discloses a protein which has a secretory leader sequence, but does not describe any subsequent cleavage events such that the full-length protein could be considered to be prepro-*mpl* ligand or pro-*mpl* ligand, and if the full-length protein is either the prepro or pro form, the specification has failed to adequately describe "mature" ligand.

Clm 9 35/39 Enablement of the current specification as filed is not commensurate in scope with claims which encompass variant forms of the particularly disclosed ligands, including functional

derivatives, fragments, alleles, isoforms and analogues thereof which have "a biological property of *mpl* ligand", as found in the definition of *mpl* ligand at page 21 of the specification. It is noted that "biological property" is defined at page 22 of the specification, as having thrombopoietic activity *or* having an in vivo effector *or* antigenic function *or* activity that is directly or indirectly caused *or* performed by an *mpl* ligand, be it native or denatured, or a fragment thereof. The specification provides adequate enablement only of the full-length, native *mpl* ligands, ligands which are truncated to consist only of the EPO-like domain, and ligands having a deletion corresponding to amino acids 111-114 of the human *mpl* ligand. While the current specification as filed discloses distinct species of protein which stimulate ^{3}H thymidine incorporation in Ba/F3-*mpl* cells and/or *in vitro* megakaryocytopoiesis, the specification does not teach how to use all possible fragments of those proteins (or even a subset thereof which would be commensurate in scope with the claims), many of which would not have biological activity, nor does the specification provide guidance as to which fragments would be reasonably expected to retain "a biological function", other than the disclosure that a soluble form of the protein consisting only of the EPO-like domain retains activity. It is noted that the envisioned scope of "fragments" as defined in the specification includes all species which are altered by either the deletion of one or more amino acids, or removal of glycosylation; however, there is no guidance in the specification as to which portions of the protein would be amenable to such deletions, nor whether or not glycosylation is required for "activity". The specification does not teach what the epitopic portions of the protein are, and in fact, does not disclose the production of any antibodies that would allow determination of such epitopic regions. Further, such language reads on mimotopes, which share antigenicity but not necessarily any sequence identity or biological activity with the disclosed protein. Further, the specification demonstrates no activity of any kind for denatured protein, nor is it predictable what activity such denatured protein would have, thus the ordinary artisan would not know how to use such, and it would require undue experimentation to determine functional denatured fragments and their appropriate uses. Therefore the specification does not teach how to make or use a number of species that would be commensurate in scope with the claims, and it would require undue experimentation practice

the invention in a manner commensurate in scope with the claims.

Enablement is also not commensurate in scope with claims to all *mpl* ligands sharing at least 80% sequence identity with the protein of Figure 8 (or portions thereof) as claimed in claim 6, or to any isolated polypeptide which is encoded by a nucleic acid which hybridizes under moderately stringent conditions to the nucleic acid sequence of Figure 8. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, catalysis and in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990. Science, Vol.247, pp.1306-1310, especially p.1306, column 2, paragraph 2). However, applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Such a definition might also read on previously characterized proteins, or alternatively, might include proteins with additional functions or activities neither envisioned nor enabled by applicants in the current invention. See Ex parte Forman, 230 U.S.P.Q. 546 (BPAI 1986) with regard to the issue raised above. With regard to the hybridization language (which, in the context of claim 9 does not have any functional limitation), first of all, it is pointed out that the term "hybridize" or "hybridization" generically refers to a process in which a strand of nucleic acid matches up with a complementary strand through the process of base pairing, wherein the process is basically used to locate or identify DNAs encoding specific proteins. It is well established in the art that 15-20 bases have been considered sufficient to achieve this

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process under stringent conditions. The conditions under which the hybridization is performed affect the outcome of the hybridization; thus, at lower stringencies, not even that much identity would be required. With these points in mind, it is the Examiner's position that giving the Claims their broadest reasonable interpretation, this language reads on an infinite number of possible DNA sequences for which there is not sufficient enablement.

Initially the process of hybridization was concerned with the isolation or identification of DNA sequences from genetically different species. As written, the Claims are not limited to polypeptides from different species nor even to mammals. In addition to the specie forms of the disclosed protein, this language encompasses proteins including: 1) biologically active *mpl* ligand, 3) inactive *mpl* ligand, 4) any of a number of fragments, derivatives, or analogs of *mpl* ligand, 5) *mpl* ligand that comprises deletions, insertions, or substitutions, 6) or unrelated or only distantly related proteins. The specification has not provided adequate description or enablement of species commensurate in scope with the claims; it would be entirely undue to determine the scope of the claims, and further determine how to make and use species commensurate with such scope.

The language of DNA "that hybridizes under moderately stringent conditions with..." literally covers all future mutations or modifications of the protein, because the disclosed sequences would be expected to hybridize to all future sequences, even those not contemplated by the Applicants at the time the Invention was made. Further, it is pointed out that this language is so broad that it would be difficult to determine what would or would not infringe the Claims. Finally, in view of the fact that the disclosed *mpl* ligand is part of a multi-gene family (as evidenced by its relatedness to EPO), it would be expected that DNA encoding other members of the family would be capable of hybridizing to the disclosed sequence, and would further encode polypeptides.

Enablement is not commensurate in scope with claims to all *mpl* ligands which are non-immunogenic in a human (re: claim 4(b)). While it would be expected that human *mpl* ligand would meet this limitation, it is unpredictable and in fact unlikely that ligand from other species would be non-immunogenic in humans in view of the fact that homologous proteins from other

Clm 4

species usually *do* cause an immunogenic reaction in humans, and the specification as filed has not taught how to make any species which would be non-immunogenic in a human other than the human isolate of *mpl* ligand itself. As stated above, there is inadequate information in the instant specification as filed with regard to the structure-function relationship of the disclosed protein to allow the ordinary artisan to predict, *a priori*, which of the innumerable possible species would be expected to be functional.

Enablement is not commensurate in scope with claims to any protein which is an *mpl* agonist as characterized in claim 5. It was found in *Ex parte Maizel* (27 USPQ2d 1662 at 1665) that:

> Appellants have not chosen to claim the DNA by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, *or* a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt,* 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it covers any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claims."

In the instant case, it is not the DNA which is being claimed, but the agonist itself, which includes in scope any protein with the stated biological function, or any other means which has such function. Clearly, the current specification as filed does not teach how to make a commensurate number of the claimed species, and in fact, fails to adequately describe a commensurate number of such species.

Finally, enablement is not commensurate in scope with claims to chimeric peptides of up to 157 hML residues substitute with one or more, but not all corresponding EPO residues as shown in Figure 9. It is noted that such language, which appears in claim 12, encompasses a number of species, n, represented by the following formula: $n=(157-35)!-1$. It would require undue experimentation to synthesize and test all such species to determine which of the several possible functions, if any, each retained, and further, the current specification as filed does not present sufficient information about the structure-function relationship of the protein, and

especially as the protein both resembles and varies from EPO, to allow the ordinary artisan to determine which species would be functional, and how to use such. Finally, it is noted that numerous of the claimed species would be more "EPO-like" than they would be "*mpl* ligand-like"; the current specification as filed does not teach how to use such "EPO-like" proteins, nor does it provide any guidance as to where the threshold between "EPO-like" and "*mpl* ligand-like" would be expected to be.

Claims 1-12, 28, 30 and 31 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 10 and 12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

X/d

It is not clear what is meant by "biologically active" in claim 10, as there is no limitation that the protein even be an *mpl* ligand, and thus fall within the definition of biological activity as given in the instant specification. Therefore, claim 10 is indefinite.

Claim 12 is indefinite as it is not clear whether the substitution of EPO residues into the hML sequence would or would not include insertion of EPO residues in positions to which there is a dash ("-") indicated in the alignment shown in Figure 9.

X/d.

Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Drop.

Claims 9 and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gerard et al. (J. Clin. Invest. 86:1921, 1990). Gerard et al. disclose a biologically active protein, mucin, which shares with the protein encoded by the nucleic acid sequence shown in Figure 8 of the instant application a stretch of 7 identical amino acid residues. These 7 residues would be encoded by a 21 base long stretch of nucleic acid including the sequence that encodes the same seven residues of the *mpl* ligand, and which, in the absence of evidence to the contrary, would reasonably be expected to hybridize under moderately stringent conditions to the nucleic acid in Figure 8; see the above discussion in the objection to the specification under 35 U.S.C. §112, first paragraph. Thus, the mucin protein of Girard et al. is an isolated polypeptide that would be encoded by a nucleic acid having a sequence that hybridizes under moderately stringent conditions to the nucleic acid molecule having the sequence shown in Figure 8.

The prior (and subsequent) art made of record and not relied upon is considered pertinent to applicant's disclosure.

Methia (Blood 82:1395, 1993) suggests that *mpl* is a cytokine receptor for a thrombopoietic cytokine and suggests using the receptor to clone the ligand. Note the ultimate paragraph (Page 1400) which indicates that it was not known whether *mpl* was a single- or multi-chain receptor.

Skoda (EMBO 12:2645, 1993) indicates that as of 1993 it was still unknown whether *mpl* had a ligand binding domain, or alternatively required a heterologous protein to form or supply the ligand binding domain (see paragraph bridging columns of page 2651).

The following patents disclose various proteins which are designated by various terms which are synonymous with thrombopoietin, none of which appear to be the same as currently claimed polypeptides, and none of which is disclosed as being an *mpl* ligand. All are disclosed as being useful for the treatment of thrombocytopenia:

U.S. Patent Number 4,894,440 (Rosenberg) discloses purified megakaryocyte-colony stimulating factor (Meg-CSF), a human protein with $M_R = 15,000$ which can be bound and eluted from WGA-Sepharose (see Col. 2). In the paragraph bridging columns 2-3, the inventors suggest cloning the Meg-CSF and propose a protocol for doing so.

U.S. Patent Number 5,326,558 (Turner et al.) discloses a human megakaryocytopoietic

factor purified from urine and then cloned. The sequences do not correspond to those of the instant specification.

U.S. Patent Number 5,260,417 (Grant et al.) disclose a megakaryocyte growth promoting activity which is a 45 kD protein.

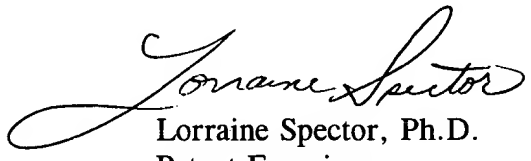
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, Ph.D. whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Garnette D. Draper, can be reached at (703)308-4232.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The Art Unit 1812 Fax Center number is (703) 308-0294. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the Examiner at the telephone number above when a fax is being transmitted.



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Patent Examiner

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